CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214900Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Sufficiency of ARIA to Evaluate the Association between Ibrexafungerp Exposure and Risks of Pregnancy, Maternal, Fetal/Neonatal and Infant Outcomes

Date:	May 27, 2021
Acting Team Leader:	Natasha Pratt, PhD Division of Epidemiology II
Deputy Director:	Monique Falconer, MD, MS Division of Epidemiology II
OPE Deputy Director:	Michael D. Blum, MD, MPH
FDA Sentinel Team Lead:	Sarah Dutcher, PhD (designee)
OSE Deputy Director:	Robert Ball, MD, MPH, ScM
Subject:	Sufficiency of ARIA to evaluate the association between ibrexafungerp exposure and risks of pregnancy, maternal, fetal/neonatal and infant outcomes.
Drug Name(s):	Brexafemme® (Ibrexafungerp)
Application Type/Number:	NDA 214900
Applicant/sponsor:	Scynexis
OSE RCM #:	2021-858

1. BACKGROUND INFORMATION

1.1. Medical Product

On February 11, 2021, the Applicant (Scynexis, Inc) submitted a new molecular entity (NME) drug application (NDA) for Ibrexafungerp, which is the first-in-class agent of a new antifungal class (triterpenoid). The proposed indication is for the treatment of vulvovaginal candidiasis (VVC) in post-menarchal women.

1.2. Describe the Safety Concern

Animal reproduction toxicity studies were conducted in both the rat and the rabbit. There were no fetal malformations detected in the rat model at the dose exposure 5 times the human exposure at the recommended human dose (RHD). However, in the rabbit model, oral ibrexafungerp administered during organogenesis was associated with rare malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the RHD.[a]

The data regarding use of ibrexafungerp in pregnant women are limited. There were four reports of pregnancies that occurred during Phases 2 and 3 of the clinical trials, one pregnancy was terminated early with no known reason and the other three resulted in live births with no known birth defects.[b]

Due the severity of the fetal toxicity findings in nonclinical studies and the benefit-risk ratio for treatment of VVC, a non-serious infection with effective alternative therapies,[c] a *contraindication (Section 4 of labeling) is added for use in pregnancy*. Ibrexafungerp labeling will also include language to verify pregnancy status prior to treatment initiation and note the fetotoxicity risk in the following sections of the label:

- ***2.*** *Dosage and Administration (subsection 2.3 Pregnancy Evaluation Prior to Initiating Treatment)*
- ***5.*** *Warnings and Precautions (subsection 5.1: Risk of Fetal Toxicity)*
- ***8.*** *Use in Specific Populations (subsections 8.1: Pregnancy; 8.3: Females and Males of Reproductive Potential [pregnancy testing and contraception])*

---

[a] In an embryo-fetal study in rabbits, ibrexafungerp was administered by oral gavage at doses of 10, 25, and 50 mg/kg/day from GD 7 through GD 19. In the mid-dose group administered 25 mg/kg/day (approximately 5 times the RHD based on AUC comparison), fetal malformations, including absent ear pinna, craniorachischisis, thoracogastroschisis, trunk kyphosis, absent forelimbs, absent forepaws, and absent hindpaw occurred in a single fetus. Malformations including absent hindpaw and anencephaly occurred with an increased litter incidence in the high-dose group of 50 mg/kg/day (approximately 13 times the RHD based on AUC comparison), and other malformations occurred in single fetuses and litters including absent ear pinna, thoracogastroschisis, absent forelimb, and absent thyroid gland. No changes in embryo-fetal survival or fetal body weights were observed with any of the ibrexafungerp doses, and fetal malformations were not observed with the 10 mg/kg/day dose of ibrexafungerp (approximately 2 times the RHD based on AUC comparison).

[b] March 29, 2021, DPMH review for Brexafemme (ibrexafungerp), Niquiche Guity., PhD, DARRTS Reference ID 4769878

[c] Vaginal candidiasis is not associated with adverse pregnancy outcomes and treatment of pregnant women is primarily indicated for relief of symptoms. The current standard of care for pregnant women is to treat VVC with topical drugs.

The Division of Pediatric and Maternal Health (DPMH) also recommends a post-marketing requirement (PMR) for a Single-Arm Pregnancy Safety Study to capture pregnancy outcomes and infant outcomes following any incidental ibrexafungerp exposures during pregnancy.[b] A single-arm pregnancy safety study is appropriate because this drug carries a contraindication and warning of fetotoxicity in the label, and the exposure during pregnancy is expected to be low. Language regarding the Pregnancy Safety Study will be included in subsection 8.1 of labeling.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

☒ Signal detection – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: *Single-arm pregnancy safety study, which enrolls exposed pregnancies into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives as needed. These broad-based surveillance studies do not require inferential analyses and do not have the sample size requirements of a traditional pregnancy registry. A single-arm pregnancy safety study is appropriate because this drug carries a contraindication and warning of fetotoxicity in the label, and the use during pregnancy is expected to be low, thus, the study is not required to be sufficiently powered for a comparative analysis.*

2.4. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to detailed narratives. This will be a descriptive broad-based surveillance study. Therefore, having detailed narratives is deemed necessary to identify and validate the outcomes, assess exposure-outcome temporality, and conduct causality assessments.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The PMR to be issued for ibrexafungerp is as follows:

Conduct a worldwide single-arm descriptive study that collects prospective and retrospective data in women exposed to Brexafemme (ibrexafungerp) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHIH-YING CHEN
05/27/2021 08:18:31 PM

MONIQUE FALCONER
05/27/2021 09:51:07 PM

MICHAEL D BLUM
05/30/2021 10:58:32 AM

SARAH K DUTCHER
06/01/2021 10:33:10 AM

ROBERT BALL
06/01/2021 10:39:13 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 21, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2020-2076-2
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader (Acting):	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 16, 2021 for Brexafemme. The Division of Anti-Infectives (DAI) requested that we review the revised container labels and carton labeling for Brexafemme (Appendix A) to determine if they are acceptable from a medication error perspective.

2 BACKGROUND

We previously evaluated the revised commercial and proposed professional container labels and carton labeling received on March 4, 2021 and did not identify areas of vulnerability that may lead to medication errors.[a]

Subsequently, on April 8, 2021, based on comments from Office of Pharmaceutical Quality (OPQ), DAI submitted an information request (IR)[b] to Scynexis to recommend revising the drug name on both the container labels and carton labeling. Additionally, the IR included a recommendation to place the strength statement "150 mg per tablet" on a separate line, immediately following the established name.

[a] Myers D. Label and Labeling Review Memo for Brexafemme (NDA 214900). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 09. RCM No.: 2020-2076-1.
[b] Rosenberger J. FDA Communication: Container Label and Carton Labeling Information Request for ibrexafungerp. Silver Spring (MD): FDA, CDER, OND, DAI (US); 2021 APR 08. NDA 214900. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805e50cf.

On April 16, 2021, Scynexis submitted their response[c] to DAI's April 8, 2021 IR, accepting DAI's recommendations and providing revised commercial and professional container labels and carton labeling, which are the subject of this review.

3 CONCLUSION

Our evaluation of the revised commercial and professional container labels and carton labeling did not identify areas of vulnerability that may lead to medication errors and we have no recommendations at this time.

[c] Cover Letter: Response to Request for Information Request for Information – Carton and Container Labeling Ibrexafungerp (NDAs 214900). Jersey City (NJ): Scynexis, Inc.; 2021 APR 16. Available at: \\CDSESUB1\evsprod\nda214900\0022\m1\us\coverletter.pdf.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
04/21/2021 12:41:08 PM

VALERIE S VAUGHAN
04/21/2021 12:48:11 PM

Clinical Inspection Summary

Date	8 April 2021
From	Cheryl Grandinetti, PharmD Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jacquelyn Rosenberger, Pharm.D., RPM Heidi Smith, MD, Medical Reviewer Thomas Smith, MD, Medical Team Leader Sumathi Nambiar, MD, Division Director Division of Anti-Infectives (DAI)
NDA #	214900
Applicant	Scynexis, Inc
Drug	Ibrexafungerp
NME	Yes
Proposed Indication	For the treatment of vulvovaginal candidiasis
Consultation Request	30 Oct 2020
Summary Goal Date	15 Apr 2021
Action Goal Date	15 Apr 2021
PDUFA Date	1 Jun 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigators, Drs. Chavoustie, Sussman, Chappell, and Livingston were inspected, and remote regulatory audits (RRAs) were conducted for two clinical investigators, Drs. Delcheva-Zantina and Bogomilov, in support of NDA 214900 (ibrexafungerp). The inspections and RRAs covered two clinical trials, SCY-078-303 and SCY-078-306. Overall, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

During the inspections and RRAs, the primary efficacy endpoint source data (i.e., the investigator's and subject's Vulvovaginal Signs and Symptoms (VSS) assessments completed at the Screening/Baseline Visit and the TOC Visit) were verified against the sponsor's data line listings for 147 out of 170 subjects (86%) randomized at these six sites. Only three single discrepancies were noted that would unlikely have an impact on the overall efficacy results. Although certified copies of the fungal culture and susceptibility test results from the central laboratories used in both studies were not available at all the clinical investigator sites, these certified copies were submitted to the NDA and verified against the sponsor's data line listings for all randomized subjects in the intent-to-treat (ITT) population at the six sites. No discrepancies were noted.

II. BACKGROUND

NDA 214900 was submitted in support of the use of ibrexafungerp for the treatment of subjects with acute vulvovaginal candidiasis. The pivotal studies supporting the application were the following:

- SCY-078-303, "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs Placebo Subjects with Acute Vulvovaginal Candidiasis"

- SCY-078-306, "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs Placebo Subjects with Acute Vulvovaginal Candidiasis"

Protocols SCY-078-303 and SCY-078-306 were identical in design and were Phase 3, multicenter, randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of oral ibrexafungerp versus placebo in subjects 12 years of age and older with acute vulvovaginal candidiasis. The primary objective of the two studies was to evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with acute vulvovaginal candidiasis by comparing the clinical outcomes of ibrexafungerp and placebo.

Protocol SCY-078-303:

- **Subjects:** A total of 371 subjects were randomized and received at least 1 dose of study drug (247 subjects received ibrexafungerp, and 124 subjects received placebo)

- **Sites:** 27 sites in the United States

- **Study initiation and completion dates:** 04 Jan 2019 (first subject, first visit) to 04 Sep 2019 (last subject, last visit)

- **Final database lock and study unblinding date:** 18 October 2019

Protocol SCY-078-306:

- **Subjects:** A total of 449 subjects were randomized and received at least 1 dose of study drug (298 subjects received ibrexafungerp, and 151 subjects received placebo)

- **Sites:** 18 sites in Bulgaria and 19 sites in the United States

- **Study initiation and completion dates:** 07 Jun 2019 (first subject, first visit) to 07 Feb 2020 (last subject, last visit)

- **Final database lock and study unblinding date:** 01 Apr 2020

Both studies consisted of the following:

- Screening visit (Day -2 to Day 1)
- Baseline visit on Day 1 (the screening and baseline visits may have occurred on the same day)
- Test-of-Cure (TOC) visit on Day 11 (± 3 days)
- Follow-Up (FU) visit on Day 25 (± 4 days)

Eligible subjects were randomized via an interactive response technology (IRT) in a 2:1 ratio to one of the following two treatment groups:

- Oral ibrexafungerp 300-mg dose BID for 1 day
- Matching placebo for Oral ibrexafungerp BID for 1 day

Subjects received their first dose of study drug at the site and received subject diaries to rate their vulvovaginal symptoms of infection and to record dosing details, adverse events, and concomitant medication use from Day 1 until the TOC visit (Day 8-Day 14). The second dose was dispensed for self-administration at home 12 hours after the first dose on Baseline (Day 1). If administering the first dose at the study center would have complicated the administration of the subsequent dose, the subject could have self-administered both doses at home to allow for a more convenient dosing schedule.

Clinical evaluation consisted of the following:

1. **Signs and Symptoms:** The signs (edema, erythema and excoriation or fissures) and symptoms (burning, itching and irritation) of infection were assessed by the investigator and the subject, respectively, on the VSS Scale.

2. **Mycological Testing:** Mycological tests included direct microscopic examination with 10% KOH and fungal cultures. At Screening (Day -2 to Day 1), a vulvovaginal specimen was obtained for direct microscopic examination with 10% KOH and was performed locally at Screening for the determination of subject eligibility and at the TOC visit (Day 8 to Day 14) or follow-up visit if symptoms persisted or recurred. Vaginal samples for fungal cultures that were collected at Screening, TOC visit, and, when possible, prior to the initiation of rescue antifungal medication during the study were also sent to a central laboratory. The central lab performed fungal cultures on the samples to determine the presence of yeast, species identification, and susceptibility testing.

3. **Safety Assessments:** Safety procedures included collection of AEs, treatment discontinuations, physical examination, vital signs, safety laboratory tests and prior and concomitant medications. Safety laboratory tests were performed by a designated central laboratory.

The ***primary efficacy endpoint*** was the percentage of subjects with clinical cure (complete resolutions of signs and symptoms) at the TOC visit (Day 8 to Day 14). Investigators and

subjects rated signs and symptoms using a VSS Scale. The VSS Scale is a standardized, predefined scale where each sign and symptom was given a numerical rating based on severity (absent = 0; mild = 1; moderate = 2; severe = 3) to calculate a total composite score.

Key secondary efficacy endpoints included the following:

- The percentage of subjects with mycological eradication (negative culture for growth of Candida species) at the TOC visit
- The percentage of subjects with complete resolution of symptoms at the FU visit.
- The absolute change in signs and symptoms score from Baseline to TOC and FU visits.

As mentioned above, a central laboratory performed fungal cultures on the vaginal samples to determine presence of yeast, species identification, and susceptibility testing. The designated central laboratories used for the protocols were as follows:

For Protocol SCY-078-303:
- NTS Ventures/Center for Medical Mycology

For Protocol SCY-078-306:
- JMI Laboratories
- IHMA, Inc.
- IHMA Europe Sarl (for sites in Bulgaria)

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history. Sites #411 and #413 are located in Bulgaria. Due to COVID-19 travel-related restrictions, on-site inspections could not be completed; therefore, remote regulatory audits (RRAs) of the study data for these two sites were conducted at: Scynexis, Inc. 1 Evertrust Plaza, 13th Floor, Jersey City, NJ 07302.

II. RESULTS (by site):

1. **Steven Chavoustie, MD**
   Site #105
   1065 Northeast 125th Street
   Suite 102
   North Miami, FL 33161
   Onsite Inspection Dates: 7 to 11 December 2020

At this site for Protocol SCY-078-306, 54 subjects were screened, 32 were randomized, and 24 subjects completed the study. Eight subjects were terminated early: three due to lack of efficacy at the TOC visit, one for not complying with the visit schedule, one for having a

positive herpes simplex virus test result, and three were lost to follow-up after the baseline visit (Subject #s (b) (6)).

An audit of the study records for the 32 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation (e.g., Form FDA 1572s, financial disclosures); primary and key secondary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint data (i.e., the investigator's and subject's VSS assessment completed at the Screening/Baseline Visit and the TOC Visit) were reviewed and verified against the sponsor's data line listings for 29 of the 32 subjects who were randomized. One discrepancy was noted at the Screening Visit for Subject # (b) (6) (randomized to ibrexafungerp): the investigator's VSS assessment in the source record was "excoriation: absent" while the sponsor's data line listings stated, "excoriation: mild."

Reviewer's comment: *This single discrepancy is unlikely to have an impact on the overall efficacy results.*

In addition, the sponsor's data line listings for fungal culture and susceptibility test results were verified against a listing of the results in an Excel spreadsheet format and sent to the clinical investigator during the inspection for the 29 of the 32 randomized subjects (i.e., the ITT population). The Excel spreadsheet was not considered to be the source record for these results because it was not the first original recording (or a certified copy of the first original recording) of the laboratory test results. In addition, the Excel spreadsheet provided to the site was neither password-protected nor contained audit trails to track any possible changes made to the test results after the first original recording of the data in the central laboratory database. Despite this, the Excel spreadsheet was used to verify the central laboratory's fungal culture and susceptibility test results against the sponsor's data line listings for the 29 randomized subjects in the ITT population. No discrepancies were noted.

Reviewer's comment*: In a 23 December 2020 response to an IR, the sponsor submitted certified copies of the fungal culture and susceptibility test results from the central laboratory to the NDA. These certified copies of the central laboratory source records were reviewed and verified against the sponsor's data listings for 29 of the 32 randomized subjects. No discrepancies were noted.*

2. Steven Sussman, MD
Site 107
123 Franklin Corner Road,
Suite 214
Lawrenceville, NJ 8648
Onsite Inspection Dates: 8 to 15 December 2020

At this site for Protocol SCY-078-303, 34 subjects were screened, 34 were randomized, and 24 subjects completed the study. Ten subjects were terminated early due to lack of efficacy or use of other antifungal therapy prior to the TOC visit. An audit of the study records for the 34 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation (e.g., Form FDA 1572s, financial disclosures); primary and key secondary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint data (i.e., VSS scales completed by the subject and the investigator at the Screening/Baseline Visit and the TOC Visit) were reviewed and verified against the data line listings provided by the sponsor for the 34 subjects who were randomized. One discrepancy for Subject # (b) (6) (randomized to ibrexafungerp) was noted: at the Screening/ Baseline Visit, the investigator's VSS assessment in the source record was "edema: absent" while the sponsor's data line listings stated "edema: mild."

Reviewer's comment: *This single discrepancy is unlikely to have an impact on the overall efficacy results.*

In addition, the sponsor's data line listings for the fungal culture and susceptibility test results were verified for all 34 randomized subjects (i.e., ITT population) against a pdf document that contained a listing of the mycology test results that was sent to the clinical investigator site during the inspection. The pdf document was not considered to be the source record for these results because it was not the first original recording (or a certified copy of the first original recording) of the laboratory test results. In addition, the pdf document provided to the site did not contain audit trails from the central laboratory database that tracked any changes made to the test results after the first original recording of the data in the central laboratory database. Despite this, the pdf document was used to verify the central laboratory's fungal culture and susceptibility test results against the sponsor's data line listings for the 34 randomized subjects in the ITT population. No discrepancies were noted.

Reviewer's comment*: In a 23 December 2020 response to an IR, the sponsor submitted certified copies of the central laboratory reports for fungal cultures and susceptibility to the NDA. These certified copies of the central laboratory source records were reviewed and verified against the sponsor's data listings for the 31 randomized subjects in the MITT population. No discrepancies were noted.*

3. Benjamin Todd Chappell, MD
Site 114
1727 Kirby Parkway, Suite 200
Memphis, TN 38120
Onsite Inspection Dates: 25 to 29 January 2021

At this site for Protocol SCY-078-303, 42 subjects were screened, 36 were randomized, and 22 subjects completed the study. Fourteen subjects were terminated early: 12 subjects due to lack of efficacy or use of other antifungal therapy prior to the TOC visit; one subject was discontinued early due to an adverse event (Subject # (b) (6) randomized to ibrexafungerp, experienced vomiting); and one subject was lost to follow-up after the baseline visit.

An audit of the study records for 15 of the 42 screened subjects was conducted—this review included 3 subjects who were screen failures and 12 subjects who were randomized. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation (e.g., Form FDA 1572s, financial disclosures); primary and key secondary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint data (i.e., VSS assessments completed by the subject and the investigator at the Screening/Baseline Visit and the TOC Visit) were reviewed and verified against the sponsor's data line listings for 12 of the 36 subjects who were randomized. No discrepancies were noted.

In addition, the sponsor provided certified copies of the central laboratory's fungal culture and susceptibility test results to the site. These certified copies were compared against the sponsor's data line listings for 8 of 22 randomized subjects in the ITT population. No discrepancies were noted.

Reviewer's comment*: In a 23 December 2020 response to an IR, the sponsor also submitted certified copies of the central laboratory reports for fungal cultures and susceptibility to the NDA. These certified copies of the central laboratory source records were reviewed and verified against the sponsor's data listings for all 35 of the 36 randomized subjects in the ITT population. No discrepancies were noted.*

4. Jeff Livingston
Site 116
3501 North MacArthur
Boulevard, Suite 600
Irving, TX 75062
Onsite Inspection Dates: 7 to 14 December 2020

At this site for SCY-078-306, 17 subjects were screened, 17 were randomized, and 13 subjects completed the study. Two subjects were terminated early due to lack of efficacy or use of other antifungal therapy prior to the TOC visit, and 2 subjects were lost to follow-up. An audit of the study records for the 17 randomized subjects was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IRB submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records, laboratory reports, and other regulatory documentation (e.g., Form FDA 1572s, financial disclosures); primary and key secondary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; and monitor logs and follow-up letters.

There was no evidence of under-reporting of adverse events. It was noted during the inspection that approximately 18% of the subjects (3 of 17 subjects) who were randomized and received study drug were ineligible to participate in the trial. Specifically, Subject #s (b) (6) (randomized to placebo) and (b) (6) (randomized to ibrexafungerp) did not meet inclusion criterion 2a [i.e., subject did not have at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline] and Subject # (b) (6) (randomized to placebo) met exclusion criteria 1 (i.e., subject had a vaginal condition other than acute vulvovaginal candidiasis that may interfere with the diagnosis or evaluation of response to therapy) of the protocol.

Reviewer's comment: *These protocol deviations were found during routine site monitoring visits, were reported to the sponsor, and were subsequently reported to FDA in Appendix 16.2.2 Protocol Deviations of the Clinical Study Report. The protocol deviations were discussed with Dr. Livingston during the inspection closeout. He acknowledged them and stated that the study staff underwent retraining on the protocol's inclusion and exclusion criteria.*

The source records for the primary efficacy endpoint data (i.e., VSS assessments completed by the subject and the investigator at the Screening/Baseline Visit and the TOC Visit) were reviewed and verified against the sponsor's data line listings provided for the 17 subjects who were randomized. No discrepancies were noted.

In addition, the sponsor's data line listings for fungal cultures and susceptibility test results were verified for all 17 randomized subjects (i.e., ITT population) against a pdf document that contained a listing of the mycology test results that was sent to the clinical investigator site during the inspection. The pdf document was not considered to be the source record for these results because it was not the first original recording (or a certified copy of the first original recording) of the laboratory test results. In addition, the pdf document provided to the site did

not contain audit trails from the central laboratory database that tracked any changes made to the test results after the first original recording of the data in the central laboratory database. Despite this, the pdf was used to verify the central laboratory's fungal culture and susceptibility test results against the sponsor's data line listings for the 17 randomized subjects in the ITT population. No discrepancies were noted.

Reviewer's comment*: In a 23 December 2020 response to an IR, the sponsor submitted certified copies of the central laboratory reports for fungal culture and susceptibility to the NDA. These certified copies of the central laboratory source records were reviewed and verified against the sponsor's data listings for the 17 randomized subjects. No discrepancies were noted.*

5. Dimka Delcheva-Zantina, MD
Site #411
1 Svoboda Square
Dupnitsa, 2600
Bulgaria
Remote Regulatory Audit (RRA) Dates: 18 to 22 December 2020

An RRA was conducted as an alternative to a foreign onsite inspection of this clinical investigator because of the travel restrictions in place due to the ongoing COVID-19 pandemic. Dr. Delcheva-Zantina authorized the RRA of the data to be conducted at the sponsor location (Scynexis, Inc., in Jersey City, NJ). The sponsor subsequently obtained certified copies of select source records for all subjects screened at this site. The sponsor was limited in the scope of source records that could be obtained for the purposes of the RRA due to the European Union's (EU) General Data Protection Regulation (GDPR) that restricts the viewing of personal information outside the European Economic Area (EEA).

At this site for Protocol SCY-078-306, per the sponsor's data line listings, 26 subjects were screened, 26 were randomized, and 23 subjects completed the study. Three subjects were terminated early due to lack of efficacy or use of other antifungal therapy prior to the TOC visit. A data audit for the 26 randomized subjects was conducted. Records reviewed included certified copies of select source records related to the primary efficacy endpoint, adverse event reporting, drug accountability, and other regulatory documents (i.e., financial disclosure, Form FDA 1572).

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint data (i.e., VSS assessments completed by the subject and the investigator at the Screening/Baseline Visit and the TOC Visit) were reviewed and verified against the data listings provided by the sponsor for the 26 subjects who were randomized. One discrepancy was noted at the TOC visit for Subject # (b) (6) (randomized to placebo): the investigator's VSS assessment in the source record was "erythema: mild" while the sponsor's data line listings stated "erythema: absent."

Reviewer's comment: *This single discrepancy is unlikely to have an impact on the overall*

efficacy results. However, it should be noted because this discrepancy occurred in a variable (i.e., investigator's VSS assessment) and a timepoint (i.e., TOC visit) used to determine the primary efficacy endpoint. The investigator's VSS assessment at the Screening/Baseline Visit was erythema: moderate, and the TOC visit assessment should have been erythema: mild (instead of erythema: absent). This subject was included in the MITT population and was assessed as a clinical cure, with symptom resolution and clinical improvement. Therefore, considering this discrepancy, it appears that this subject should have been categorized with "symptom persistence."

The sponsor's data line listings for fungal culture and susceptibility test results could not be verified for any of the subjects during this RRA as these source records were not available for review.

Reviewer's comment*: In a 23 December 2020 response to an IR, the sponsor submitted certified copies of the central laboratory reports for fungal cultures and susceptibility to the NDA. These certified copies of the central laboratory source records were reviewed and verified against the sponsor's data line listings for the 26 randomized subjects (i.e., the ITT population). No discrepancies were noted.*

6. Eduard Bogomilov, MD
Site #413
2 Kableshkov street
Lom, 3600
Bulgaria
RRA Dates: 8 to 11 December 2011

An RRA was conducted as an alternative to a foreign onsite inspection of this clinical investigator because of the travel restrictions in place due to the ongoing COVID-19 pandemic. Dr. Bogomilov authorized the RRA of the data to be conducted at the sponsor location (Scynexis, Inc., in Jersey City, NJ). The sponsor subsequently obtained certified copies of select source records for all subjects screened at this site. The sponsor was limited in the scope of source records that could be obtained for the purposes of the RRA due to the EU GDPR that restricts the viewing of personal information outside the EEA.

At this site for Protocol SCY-078-306, per the sponsor's data line listings, 29 subjects were screened, 29 were randomized, and 26 subjects completed the study. Three subjects were terminated early due to lack of efficacy or use of other antifungal therapy prior to the TOC visit. A data audit for the 29 randomized subjects was conducted. Records reviewed included certified copies of select source records related to the primary efficacy endpoint, adverse event reporting, drug accountability, and other regulatory documents (e.g., financial disclosure, Form FDA 1572).

There was no evidence of under-reporting of adverse events. The source records for the primary efficacy endpoint data (i.e., VSS assessments completed by the subject and the investigator at the Screening/Baseline Visit and the TOC Visit) were reviewed and verified

against the data line listings provided by the sponsor for the 29 subjects who were randomized. No discrepancies were noted.

The sponsor's data line listings for fungal culture and susceptibility test results could not be verified for any of the subjects during this RRA as these source records were not available for review.

***Reviewer's comment**: In a 23 December 2020 response to an IR, the sponsor submitted certified copies of the central laboratory reports for fungal cultures and susceptibility to the NDA. These certified copies of the central laboratory source records were reviewed and verified against the sponsor's data listings for the 29 randomized subjects (i.e., the ITT population). No discrepancies were noted.*

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 214900
DAI /Project Manager/Jacquelyn Rosenberger
DAI/Clinical Reviewer/Heidi Smith
DAI/Clinical Team Leader/ Thomas Smith
DAI/Division Director/Sumathi Nambiar
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHERYL A GRANDINETTI
04/08/2021 07:31:45 AM

PHILLIP D KRONSTEIN
04/08/2021 08:48:15 AM

KASSA AYALEW
04/08/2021 01:43:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: March 29, 2021 **Date consulted:** February 11, 2021

From: Niquiche Guity, Ph.D, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Anti-Infectives (DAI)

Drug: Brexafemme (Ibrexafungerp) 150mg oral tablets

NDA: 214900

Applicant: Scynexis Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Treatment of vulvovaginal candidiasis

Materials Reviewed:

- DPMH consult request dated February 11, 2021, DARRTS reference ID 4746212
- NDA 214900, Module 4.2.3.5.2 Embryo-fetal development toxicology study reports
- proposed labeling for NDA 214900 for Ibrexafungerp

Consult Question:
DAI is seeking assistance from DPMH in developing the product labeling to provide a clear risk summary for oral ibrexafungerp use by women of child-bearing potential. The findings of phocomelia and anencephaly occurred only in a single species and at doses in excess of the maximum recommended dose. However, given these findings are severe and are rare in embryo-fetal toxicity studies of other anti-infective agents, we believe these require significant changes to product labeling.

Specific questions:

- DAI is strongly considering the addition of a warning for embryo-fetal toxicity in Section 5 – does DPMH agree?
- If a warning is added, should the indication statement be updated to include only non-pregnant females?
- Does DPMH recommend the addition of a contraindication for use in pregnancy?
- How would DPMH recommend these findings be incorporated into the risk summary in Section 8.1?

INTRODUCTION AND BACKGROUND
On February 11, 2021, the applicant (Scynexis, Inc) submitted a new molecular entity (NME) drug application (NDA) for Ibrexafungerp for the treatment of vulvovaginal candidiasis. The Division of Anti-Infectives (DAI) consulted the Division of Pediatric and Maternal Health (DPMH) on February 11, 2021, to assist with the Pregnancy and Lactation subsections of labeling. Ibrexafungerp is proposed to be the first-in-class of a new class of antifungal agents (triterpenoid) for the treatment of vulvovaginal candidiasis.

Table 1: Drug Characteristics[1,2]

Drug class	a triterpenoid antifungal agent
Mechanism of action	inhibits glucan synthase, an enzyme involved in the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall.
Dose and administration	300 mg (two tablets of 150 mg) twice a day for one day, for a total treatment dosage of 600 mg.
Molecular weight	922.18 grams per mole.
Protein Binding	>99%
Half-life	20 hours
Serious adverse reactions	Hypersensitivity to ibrexafungerp or any of its components.
Adverse reactions	diarrhea, nausea, and abdominal pain, dizziness and vomiting

[1] Azie N, Angulo D, Dehn B, Sobel JD. Oral Ibrexafungerp: an investigational agent for the treatment of vulvovaginal candidiasis. Expert Opin Investig Drugs. 2020 Sep;29(9):893-900. doi: 10.1080/13543784.2020.1791820. Epub 2020 Aug 19. PMID: 32746636.
[2] https://pubchem.ncbi.nlm.nih.gov/compound/Ibrexafungerp-citrate

REVIEW

PREGNANCY

Vulvovaginal candidiasis (VVC) and Pregnancy[3,4]

- **Description:** Characterized inflammation due to the overgrowth of the Candida species that results in the common vaginitis symptoms of itching and erythema.
- **Incidence:** Second most common cause of vaginitis symptoms and accounts for approximately one-third of vaginitis cases. Although the prevalence is difficult to determine as candida species are part of the normal flora of approximately 25 percent of women, most studies suggest a VVC prevalence of 5–15% depending on the population studied. It is estimated 70–75% of females will have at least one episode of VVC during their lives while 40–50% will experience a recurrence.[5]
- **Risk Factors:** Diabetes mellitus, antibiotic use, increased estrogen levels (e.g., pregnancy and postmenopausal estrogen therapy), immunosuppression, genetic polymorphisms in SIGLEC15 gene (produces a cell surface protein found on macrophages and dendritic cells), TLR2 (plays a fundamental role in pathogen recognition and activation of innate immunity) and mannose-binding lectin genes (plays a key role in the human innate immune response)
- **Symptoms** - Vulvar pruritus, vulvar burning, soreness, and irritation are also common and can be accompanied by dysuria or dyspareunia
- **Treatments –**
    - Healthy non-pregnant women
        - Oral treatment (e.g., Fluconazole/Diflucan, ketoconazole) or topical anti-fungal treatments (e.g., clotrimazole, miconazole, terconazole)
    - Pregnant women
        - topical imidazole (clotrimazole or miconazole) vaginally for seven days rather than treatment with an oral azole because of potential risks with oral azole therapy in pregnancy (risk of miscarriage during first trimester and impact on birth defects is unclear). Treatment of pregnant women is primarily indicated for relief of symptoms as vaginal candidiasis is not associated with adverse pregnancy outcomes.

Nonclinical Experience

In an embryo-fetal study in rabbits, ibrexafungerp was administered by oral gavage in doses of 10, 25, and 50 mg/kg/day from GD 7 to GD 19. No changes in embryo-fetal survival or fetal body weights were observed with any of the ibrexafungerp doses and fetal malformations and variations were not observed with the 10 mg/kg/day dose of ibrexafungerp (approximately equal to 2 times the maximum recommended dose based on AUC comparison). In the mid-dose group administered 25 mg/kg/day ibrexafungerp (approximately equal to 5 times the recommended

[3] https://www.uptodate.com/contents/candida-vulvovaginitis-clinical-manifestations-and-diagnosis?source=history_widget

[4] Bruna Gonçalves, Carina Ferreira, Carlos Tiago Alves, Mariana Henriques, Joana Azeredo & Sónia Silva (2016) Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors, Critical Reviews in Microbiology, 42:6, 905-927, DOI: 10.3109/1040841X.2015.1091805

[5] Sobel J. Current Treatment Options for Vulvovaginal Candidiasis. Women's Health. September 2005:253-261. doi:10.2217/17455057.1.2.253

human dose based on AUC comparison), fetal malformations including absent ear pinna, general body craniorachischisis, trunk kyphosis, absent hindpaw, and forelimb phocomelia occurred in single fetus but not in fetuses in the vehicle control group or in comparable historical control data. Malformations including absent hindpaw and anencephaly occurred with an increased litter incidence in the high-dose group of 50 mg/kg/day (approximately equal to 13 times the maximum recommended dose based on AUC comparison) as well as other malformations that occurred in single fetuses but not in comparable historical control data including absent ear pinna, forelimb phocomelia, and absent thyroid gland.

In a rat embryo-fetal study, ibrexafungerp was administered to pregnant rats by oral gavage from gestation days (GDs) 6 through 17 in dosages of 10, 20, 35, and 50 mg/kg/day. No changes in embryo-fetal survival, fetal body weights, or fetal malformations and variations occurred up to the high-dose of 50 mg/kg/day ibrexafungerp (approximately equal to 5 times the recommended human dose based on plasma AUC comparison).

In a pre-postnatal study in rats, ibrexafungerp was administered by oral gavage from GD 6 through the lactation period until (LD) 20 in maternal doses of 10, 20, 35, and 50 mg/kg/day. No adverse effects on the survival, growth, behaviour, or reproduction of first-generation offspring occurred with any of the ibrexafungerp doses up to the high dose of 50 mg/kg/day (approximately 5 times the recommended human dose based on AUC comparison).

For full details, please see the Pharmacology/Toxicology review by James Wild, PhD.

Review of Pharmacovigilance Database

In the Phase 2 and 3 trials of VVC treatment, three subjects and one subject became pregnant within 10 days and five weeks, respectively, of oral ibrexafungerp dosing. One of the pregnancies that occurred within 10 days of oral ibrexafungerp dosing was electively terminated with no known reason; the other three pregnancies resulted in live births with no known birth defects.

Review of Literature[6,7,8,9]

DPMH conducted a search of published literature search for “ibrexafungerp” and “pregnancy” and “congenital defects/congenital anomalies/teratogenicity/prematurity/stillbirth/spontaneous abortion/miscarriage” and did not identify any publications.

Ibrexafungerp is not referenced in Micromedex, ReproTox, or TERIS databases.

Reviewer’s comment:
Overall, the applicant performed an adequate summary of their clinical trial database regarding ibrexafungerp use during pregnancy. As this is a new molecular entity (NME), the applicant noted that there are limited data on ibrexafungerp use in pregnant women to evaluate for drug-associated risks of birth defects, miscarriages, or adverse maternal or fetal

[6] https://www.micromedexsolutions.com, accessed 3/1/21.
[7] https://pubmed ncbi nlm nih.gov/, accessed 3/1/21
[8] https://www.embase.com/, accessed 3/1/21
[9] Brigg’s Drugs in Pregnancy and Lactation, accessed 3/15/21

outcomes. The applicant's conclusion is appropriate based on the review of the literature for ibrexafungerp.

LACTATION

Nonclinical Experience

No animal lactation studies have been performed.

Review of Pharmacovigilance Database

There are no reports of ibrexafungerp exposure during lactation in the clinical trials.

Review of Literature[4,5,6,7]

DPMH conducted a search in PubMed and Embase using the search terms "ibrexafungerp" AND "lactation/breastfeeding" did not identify any articles.

Ibrexafungerp is not referenced in ReproTox, TERIS, LactMed, or Thomas Hale's Book (Medications and Mothers' Milk[10]).

Reviewer comment:

The applicant stated that "*There is no information on the presence of ibrexafungerp in human milk, the effects on the breastfed infant, or the effects on milk production. The expression of ibrexafungerp in human milk has not been studied." This is an NME; therefore, the applicant did not conduct a review of published literature. Based on the review of the literature, the applicant's findings are agreeable.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

The applicant performed male and female fertility study in rats. Ibrexafungerp was administered to male rats by oral gavage in doses of 10, 20, 40, and 80 mg/kg/day for 28 days before mating and throughout mating and to female rats for 15 days before mating, during mating, and until gestation day (GD) 6. Ibrexafungerp did not impair fertility in either sex at any dose up to the highest dose of 80 mg/kg/day (approximately 10 times the recommended human dose based on AUC comparison).

Review of Pharmacovigilance Database

The applicant reported the fertility status as part of the baseline characteristics for ibrexafungerp clinical trials. There were no reports any cases of infertility in clinical trials conducted for ibrexafungerp.

Review of Literature

DPMH conducted a search of published literature using the search terms "ibrexafungerp" AND "fertility/infertility/reproduction/sperm" and did not identify any relevant publications.

Reviewer comment:

While the applicant only reported the fertility status as part of the baseline characteristics for clinical trials, review of the literature did not produce any relevant findings related to

[10] Hale TW. Hale's medications and mother's milk. 2019. Springer Publishing Co. NY, New York.

reproductive potential/fertility. Therefore, based on the review of the literature, the information presented by the applicant appears to be sufficient.

DISCUSSION AND CONCLUSIONS

Pregnancy

The data regarding use of BREXAFEMME (ibrexafungerp) in pregnant women are very limited. There were four reports of pregnancies that occurred during Phases 2 and 3 of the clinical trials, one pregnancy was terminated early with no known reason and the other three resulted in live births with no known birth defects. The sample size is very small and does not provide enough information to draw any substantial conclusions about adverse pregnancy and infant outcomes. Animal reproduction toxicity studies were conducted in both the rat and the rabbit. There were no fetal malformations detected in the rat model at the dose exposure 5 times the human exposure at the recommended human dose (RHD). However, in the rabbit model, severe external, visceral, and skeletal malformations including forelimb phocomelia, multiple malpositioned organs, and multiple absent skull bones were associated with dose exposures greater or equal to approximately 5 times the human exposure at the RHD of ibrexafungerp.

DPMH met with the DAI nonclinical and clinical teams to discuss the results of the nonclinical findings. Despite the lack of findings in the rat studies, the nonclinical team expressed their concern regarding the severe malformations that were detected within the mid and high doses of ibrexafungerp (greater or equal to approximately 5 times the human exposure at the RHD) in the embryofetal toxicity rabbit study. They stated that these severe malformations are only seen rarely in anti-infective agents and that it was not unusual to have malformations in one species but not the other. For example, thalidomide which is known to cause phocomelia in humans does not show fetal malformations in most strains of rats but showed fetal malformations in the rabbit model similar to the malformations seen in humans.[11] Additionally, the nonclinical team consulted with another internal pharmacology/toxicology group, the PTCC Reproductive Toxicology Subcommittee to solicit feedback as to whether the associated fetal malformations in the rabbits were attributed to ibrexafungerp. The consensus from the PTCC Reproductive Toxicology Subcommittee was that the malformations observed in the rabbit model suggested that the effects on the fetus were directly related to the drug treatment rather than exposure to maternal toxicants since the malformations seen were similar between the mid and high drug dosages, and the only effect seen on the mother appeared to be related to reduced weight gain (with no corresponding effect on absolute weights) occurring during the first few days of treatment. Literature suggests that you need extensive reductions in food consumption with associated effects of prolonged weight loss/absence of weight gain to induce malformations which was not seen in the ibexafungerp embryo-fetal rabbit study.[12] Furthermore, PTCC Reproductive Toxicology Subcommittee stated that with rabbits you are more likely to see increased resorptions if the doe is sensing poor conditions during pregnancy.[13] Therefore,

[11] Janer G, Slob W, Hakkert BC, Vermeire T, Piersma AH. A retrospective analysis of developmental toxicity studies in rat and rabbit: what is the added value of the rabbit as an additional test species? Regul Toxicol Pharmacol. 2008 Mar;50(2):206-17. doi: 10.1016/j.yrtph.2007.11.007. Epub 2007 Nov 28. PMID: 18171599.

[12] Cappon GD, Fleeman TL, Chapin RE, Hurtt ME. Effects of feed restriction during organogenesis on embryo-fetal development in rabbit. Birth Defects Res B Dev Reprod Toxicol. 2005 Oct;74(5):424-30. doi: 10.1002/bdrb.20058. PMID: 16249998.

[13] Email communication on 2/25/2021 from James Wild Ph.D., noncinical reviewer

DPMH agreed with both the clinical team and nonclinical team, that a warning statement would be appropriate for this drug labeling.

To determine the most appropriate warning (e.g., boxed warning, warnings and precautions statement or contraindication) for this labeling, a comparison of labelings within the drug class (anti-fungal), dosage administration, drugs contraindicated for pregnancy, or drugs with a boxed warning for pregnancy was conducted. (See Appendix 1, Table 2.) Mostly labelings convey the concern derived from animal studies through the *"Warnings and Precautions*" section or with a *"Boxed Warning"*. Generally, contraindications were reserved when human data identified adverse effects of the drug. Vaginal candidiasis is not associated with adverse pregnancy outcomes and treatment of pregnant women is primarily indicated for relief of symptoms. The current standard of care for pregnant women is to treat VVC with topical drugs. Additionally, limited human pregnancy data collected in the study revealed no malformations in the fetus that were carried to term and Brexafemme exposure will be limited to administration twice a day for one day with elimination from the body after four days. However, due to the severity of the malformations (e.g., phocomelia) seen in the embryofetal toxicity rabbit study, which was reminiscent of the thalidomide drug history where the fetal malformations were seen in only one animal model and the alternative topical treatments that are available for VVC in pregnancy, DPMH recommends adding a Warning and Precaution statement to the labeling. DAI continues to consider the appropriateness of a boxed warning.

Furthermore, DPMH recommends issuing a postmarketing requirement (PMR) for a Single-Arm Pregnancy Safety Study to capture pregnancy outcomes and infant outcomes following any incidental ibrexafungerp exposures during pregnancy. For the single-arm safety pregnancy safety study, the applicant would be required to use a structured approach to data collection and targeted questionnaires throughout pregnancy to obtain follow-up information on all ibrexafungerp-exposed pregnancies of which they become aware. The reader is referred to the FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies: Considerations for Study Design, published May 2019, for further details.

Lactation

There is no information regarding the use of ibrexafungerp in lactating animals or humans. The drug's characteristics (>90% bound to serum albumin and MW 922 .18 daltons) suggest that low levels may be present in human breast milk. Therefore, DPMH recommends using the standard risk/benefit language in subsection 8.2 of BREXAFEMME labeling.

DPMH recommends a postmarketing milk-only clinical lactation study as there is anticipated use of BREXAFEMME in females of reproductive potential. The clinical lactation study would assess the amount of drug present in human milk to better inform recommendations for use of ibrexafungerp in lactating women. Refer to the FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design, published May 9, 2019.[14]

[14] For more information about Postapproval Pregnancy Safety Studies PMR Considerations and Case Examples, refer to the document on the MHT Drive: "Post-marketing pregnancy and lactation study checklists" → "Lactation PMR Checklist" → "Final Version→ "Lactation Study PMR Checklist 3.31.2020"

Females and Males of Reproductive Potential

There are no data on ibrexafungerp and its effects of fertility in humans. Animal data do not demonstrate any effects on fertility. However, due to ibrexafungerp's potential for fetal toxicity, pregnancy testing and contraception recommendations will be included in subsection 8.3, Females and Males of Reproductive Potential. Contraception recommendations use of 4 days after last dose are based on the drug's half-life of 20 hrs.

LABELING RECOMMENDATIONS

DPMH provided language for warnings and precautions and subsections 2.3, 5.1, 8.1, 8.2, 8.3, and section 17 of the BREXAFEMME labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on March 10, 2021. DPMH recommendations are below and reflect the discussions with DAI. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Fetal Toxicity: May cause fetal harm. (b) (4) Advise females of reproductive potential to use effective contraception. (2.3, 5.1, 8.1, 8.3)

FULL PRESCRIBING INFORMATION

FULL PRESCRIBING INFORMATION

2 Dosage and Administration

2.3 Pregnancy Testing

(b) (4) in females of reproductive potential prior to initiating therapy with BREXAFEMME *[see Warning and Precautions (5.1)]*.

5.1 Fetal Toxicity

Based on findings from animal studies, BREXAFEMME may cause fetal harm (b) (4) In animal reproduction studies, ibrexafungerp administered orally to pregnant rabbits during organogenesis was associated with (b) (4) fetal malformations (b) (4) at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose. (b) (4)

Prior to initiating therapy with BREXAFEMME, verify the pregnancy status of females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after last dose *[see Use in Specific Populations (8.1, 8.3)* (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies, BREXAFEMME may cause fetal harm (b) (4) . In pregnant rabbits, oral ibrexafungerp administered during organogenesis was associated with multiple rare (b) (4) at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose (RHD). Oral Ibrexafungerp administered to pregnant rats during organogenesis was not associated with fetal toxicity or increased fetal malformations at a dose exposure approximately 5 times the human exposure at the RHD *(see Data)*. Available data on BREXAFEMME use in pregnant females are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. (b) (4)

(b) (4)

Data

Animal Data

In a rat embryo-fetal study, ibrexafungerp was administered to pregnant rats by oral gavage from gestation days (GDs) 6 through 17 in dosages of 10, 20, 35, and 50 mg/kg/day. (b) (4) up to the high-dose of 50 mg/kg/day (approximately 5 times the recommended human dose based on plasma AUC comparison).

In an embryo-fetal study in rabbits, ibrexafungerp was administered by oral gavage in doses of 10, 25, and 50 mg/kg/day from GD 7 through GD 19. In the mid-dose group administered 25 mg/kg/day ibrexafungerp (approximately (b) (4) 5 times the recommended human dose based on AUC comparison), fetal malformations (b) (4)

(b) (4)

No changes in embryo-fetal survival or fetal body weights were observed with any of the ibrexafungerp doses and fetal malformations (b) (4) were not observed with the 10 mg/kg/day dose of ibrexafungerp (approximately equal to 2 times the maximum recommended dose based on AUC comparison).

In a pre-postnatal study in rats, ibrexafungerp was administered by oral gavage from GD 6 through the lactation period until (LD) 20 in maternal doses of 10, 20, 35, and 50 mg/kg/day. No maternal toxicity or adverse effects on the survival, growth, behavior, or reproduction of first-generation offspring occurred with any of the ibrexafungerp doses up to the high dose of 50 mg/kg/day (approximately 5 times the recommended human dose based on AUC comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of ibrexafungerp in either human or animal milk, the effects on the breast-fed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BREXAFEMME and any potential adverse effects on the breastfed child from BREXAFEMME or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating (b) (4) with BREXAFEMME.

Contraception

Females

(b) (4) Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after last dose.

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

(b) (4) Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception while taking BREXAFEMME and for 4 days after last dose *[see Use in Specific Populations (8.3)]*.

Appendix 1: Table 2: Labeling Comparison

Drug	Indication	Dosage	Animal studies - toxicity reported	Human toxicity reported	Highlights Section - Use in Specific Population	Boxed Warning	Contraindications	Warnings and Precautions
Vancomycin	• Clostridioides difficile-associated diarrhea	• 125 mg orally 4x daily for 10 days.	• No • rats • rabbits	no	no	no	no	no
Micafungin	• Treatment of Candidemia • Acute Disseminated Candidiasis • Candida Peritonitis and Abscesses	• 100 mg range up to 10 to 47 days	• yes • rabbits (4x RHD)	no	yes	no	no	no
Flucytosine	• Serious Candida or Cryptococcal infections	• 50 to 150 mg/kg/day administered in divided doses at 6-hour intervals	• rats (0.89x RHD) • rabbits (No) • mice (0.236x RHD)	no	n/a	no	no	no

Drug	Indication	Dosage	Animal studies - toxicity reported	Human toxicity reported	Highlights Section - Use in Specific Population	Boxed Warning	Contraindications	Warnings and Precautions
Fluconazole	• VVC • Oropharyngeal/esophageal candidiasis • Cryptococcal meningitis • Prophylaxis in BMT	• 150 mg as a single oral dose	• yes • rabbits (4x RHD) • rats (2x RHD)	yes	n/a	no	no	yes
Voriconazole	• Invasive aspergillosis • Candidemia/ other deep tissue infections • Esophageal candidiasis • Serious infections due Scedosporium or Fusarium refractory/intolerant of other Rx	• 200 mg for at least 14 days	• yes, • rats (0.3x RHD) • rabbits (6x RHD)	no	no	no	no	yes

Drug	Indication	Dosage	Animal studies - toxicity reported	Human toxicity reported	Highlights Section - Use in Specific Population	Boxed Warning	Contraindications	Warnings and Precautions
Telavancin	• Complicated skin and skin structure infections (cSSSI), • Hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP)	• cSSSI -10 mg/kg by IV infusion over 60 minutes every 24 hours for 7 to 14 days • HABP/VABP - 10 mg/kg by IV infusion over 60 minutes every 24 hours for 7 to 21 days	• yes • rats rabbits mimipigs (1-2x RHD)	no	no	yes	no	yes
Isotretinoin	• severe recalcitrant nodular acne in non-pregnant patients > 12 years of age	• 0.5 to 1 mg/kg/day given in two divided doses with or without meals for 15 to 20 weeks	no	yes	no	yes	yes	no
Methotrexate	• severe, active rheumatoid arthritis (RA), • polyarticular juvenile idiopathic arthritis (pJIA), • disabling psoriasis	• Adult RA: 7.5 mg once weekly. • pJIA: 10 mg/m2 once weekly.	no	yes	no	yes	yes	no

Drug	Indication	Dosage	Animal studies - toxicity reported	Human toxicity reported	Highlights Section - Use in Specific Population	Boxed Warning	Contraindications	Warnings and Precautions
Lomitapide	• an adjunct to a low-fat diet and other lipid-lowering treatments	• Initiate treatment at 5 mg once daily. increase to 10 mg daily after at least 2 weeks; and then 20 mg, 40 mg/4 week interval, and maximum recommended dose of 60 mg daily	• yes • rats (RHD) • ferrets (<RHD) • rabbits (6x RHD)	no	no	no	yes	yes
Thalidomide	• multiple myeloma (MM) • erythema nodosum leprosum (ENL)	• MM: 200 mg orally once daily, • ENL 100 to 300 mg/day for an episode of cutaneous	• yes • rats • rabbits (1.5x RHD)	yes	no	yes	yes	yes

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIQUICHE M GUITY
03/29/2021 01:01:20 PM

LYNNE P YAO
03/29/2021 03:55:03 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 9, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
OSE RCM #:	2020-2076-1
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Team Leader (Acting):	Valerie Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label and carton labeling, as well as a proposed professional sample container label and carton labeling, received on March 4, 2021, for Brexafemme. The Division of Anti-Infectives (DAI) requested that we review the container labels and carton labeling for Brexafemme (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review, as well as comments from our Office of Pharmaceutical Quality (OPQ) colleagues.[a,b]

2 ANALYSIS AND DISCUSSION

Scynexis included in their response, to our information request dated February 19, 2020, that their expiration date format will be shown as "YYYY-MM-DD" with all numerical characters.[c] Additionally, Scynexis has revised the storage statement to read "Store BREXAFEMME tablets at

[a] Myers, D. Label and Labeling Review for Brexafemme (NDA 214900). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 27. RCM No.: 2020-2076.
[b] Rosenberger, J. FDA Communication: NDA 214900 [ibrexafungerp] Carton and Container Labeling: FDA, CDER, OND, DAI (US); 2021 FEB 19. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805d4057.
[c] Cover Letter: Response to Request for Information for ibrexafungerp (NDA 214900). Jersey City (NJ): Scynexis, Inc.; 2021 MAR 04. Available at: \\CDSESUB1\evsprod\nda214900\0016\m1\us\coverletter.pdf.

room temperature 20°C to 25°C (68°F to 77°F)," on the carton and to "Store at 25°C (77°F), see insert." on the blister card. (b) (4) [redacted] We defer to the Office of Pharmaceutical Quality (OPQ) to determine the appropriateness of these proposed changes to the storage statements.

3 CONCLUSION

The Applicant implemented all of our recommendations to their proposed commercial container label and carton labeling and we have no additional recommendations at this time. Additionally, our evaluation of the proposed professional sample container label and carton labeling did not identify areas of vulnerability that may lead to medication errors and we have no recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
03/09/2021 03:39:47 PM

VALERIE S VAUGHAN
03/09/2021 04:40:13 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 8, 2021

To: Jacquelyn Rosenberger, PharmD, RAC
Regulatory Health Project Manager, Division of Anti-Infectives (DAI)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for BREXAFEMME™ (ibrexafungerp) tablets, for oral use

NDA: 214900

In response to DAI's consult request dated November 24, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for BREXAFEMME™ (ibrexafungerp) tablets, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAI (Jacquelyn Rosenberger) on February 22, 2021 and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on March 2, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 4, 2021 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or carrie.newcomer@fda.hhs.gov.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE A NEWCOMER
03/08/2021 02:26:07 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 2, 2021
To:	Jacquelyn Rosenberger Regulatory Project Manager **Division of Anti-Infectives (DAI)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	James Dvorsky, PharmD **Team Leader** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	BREXAFEMME (ibrexafungerp)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214900
Applicant:	Scynexis, Inc.

1 INTRODUCTION

On October 1, 2020, Scynexis, Inc. submitted for the Agency's review an original New Drug Application (NDA) 214900 for TRADENAME (ibrexafungerp) tablets, for oral use, a New Molecular Entity (NME), for the proposed indication of the treatment of vulvovaginal candidiasis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on November 24, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (ibrexafungerp) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (ibrexafungerp) PPI received on October 1, 2020, and received by DMPP and OPDP on November 24, 2020.
- Draft TRADENAME (ibrexafungerp) Prescribing Information (PI) received on October 1, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 22, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E CARROLL
03/02/2021 09:36:02 AM

JAMES S DVORSKY
03/02/2021 01:15:08 PM

MARCIA B WILLIAMS
03/02/2021 01:38:55 PM

LASHAWN M GRIFFITHS
03/02/2021 01:48:27 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 27, 2021
Requesting Office or Division:	Division of Anti-Infectives (DAI)
Application Type and Number:	NDA 214900
Product Name and Strength:	Brexafemme (ibrexafungerp) Tablets, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Scynexis, Inc. (Scynexis)
FDA Received Date:	October 1, 2020 and October 30, 2020
OSE RCM #:	2020-2076
DMEPA Safety Evaluator:	Deborah Myers, RPh, MBA
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for Brexafemme (ibrexafungerp) Tablets, the Division of Anti-Infectives (DAI) requested that we review the proposed Brexafemme prescribing information (PI), container label (blistercard of 4 tablets), and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container label (blistercard of 4 tablets), and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 *How Supplied/Storage and Handling*			
1.	As currently presented, the associated	Per USP[a], the Centigrade temperature(s) precede the	To provide clarity and consistency with the storage

[a] USP General Chapter <659> Packaging and Storage Requirements.

Table 2. Identified Issues and Recommendations for Division of Anti-Infectives (DAI)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Centigrade temperatures are not included in the proposed storage statement, (b) (4) [redacted]	Fahrenheit temperature(s) in storage statements. Additionally, the use of a non-standard storage statement could result in improperly storing of this product leading to deteriorated drug medication errors.	statement, revised the current text such that the associated Centigrade temperature range precedes the Fahrenheit temperature range. For example, "Store BREXAFEMME tablets at 20°C to 25°C (68°F to 77°F) (b) (4) [redacted] Additionally, we defer to The Office of Pharmaceutical Quality (OPQ) to confirm that the above revision is accurate and an appropriate recommendation for inclusion on the carton labeling (see Carton Labeling recommendation #1 below).

Table 3. Identified Issues and Recommendations for Scynexis, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label (blistercard of 4 tablets) and Carton Labeling			
1.	As currently presented, the human-readable format for expiration date is not clearly defined (e.g., "XXXXX" is notated as the intended expiration date format on the proposed container label (blistercard of 4 tablets)).	Clearly defining of the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are

Table 3. Identified Issues and Recommendations for Scynexis, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	As currently presented, the strength statement on the container label (blistercard of 4 tablets) and carton labeling is "150 mg."	Wrong dose medication errors could occur if users misinterpret the strength statement (i.e., 150 mg) on the container label (blistercard of 4 tablets) and carton labeling as the total strength of the package contents (i.e., 150 mg (4 x 150 mg tablets)), instead of the strength of a single tablet.	To address the risk of misinterpretation of the strength statement and to provide consistency throughout the package labeling (i.e., container label (blistercard of 4 tablets) and carton labeling), we recommend revising all occurrences of the strength statement "150 mg" to "150 mg per tablet" using consistent size and color of the font. Or you may instead consider changing the current "BREXAFEMME ibrexafungerp tablet, 150 mg" to instead (BREXAFEMME (ibrexafungerp) 150 mg per tablet."
Carton Labeling			

Table 3. Identified Issues and Recommendations for Scynexis, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	As currently presented, the associated Centigrade temperatures are not included in the proposed storage statement (b) (4) [redacted]	Per USP[b], the Centigrade temperature(s) precede the Fahrenheit temperature(s) in storage statements. Additionally, the use of a non-standard storage statement could result in improperly storing of this product leading to deteriorated drug medication errors.	To provide clarity and consistency with the storage statement, revise the current text such that the associated Centigrade temperature range precedes the Fahrenheit temperature range. For example, "Store BREXAFEMME tablets at room temperature 20°C to 25°C (68°F to 77°F (b) (4) [redacted]

4 CONCLUSION

Our evaluation of the proposed Brexafemme prescribing information (PI), container label (blistercard of 4 tablets), and carton labeling, identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Scynexis, Inc. so that recommendations are implemented prior to approval of this NDA.

[b] USP General Chapter <659> Packaging and Storage Requirements.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Brexafemme that Scynexis, Inc. submitted on October 30, 2020.

Table 4. Relevant Product Information for Brexafemme	
Initial Approval Date	N/A
Active Ingredient	ibrexafungerp
Indication	For the treatment of (b) (4) adult women with vulvovaginal candidiasis (VVC), also known as vaginal yeast infection.
Route of Administration	Oral
Dosage Form	Tablets
Strength	150 mg
Dose and Frequency	300 mg (two tablets of 150 mg) twice a day for one day, for a total treatment dosage of 600 mg
How Supplied	blister packs, four (4) tablets per pack
Storage	Store at 68°F to 77°F (b) (4)
Container Closure	A polyvinyl chloride/polyvinylidene chloride blister foil sealed with a push through (b) (4) aluminum foil. The blister is heat sealed onto a child resistant (CR), (b) (4) (b) (4) The blister card is enclosed in a standard box carton.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Brexafemme labels and labeling submitted by Scynexis, Inc..

- Container label (blistercard of 4 tablets) received on October 1, 2020
- Carton labeling received on October 1, 2020
- Prescribing Information and Patient Information received on October 30, 2020, available at the following link: \\CDSESUB1\evsprod\nda214900\0003\m1\us\draft-brexafemme-plr-label-final.docx.

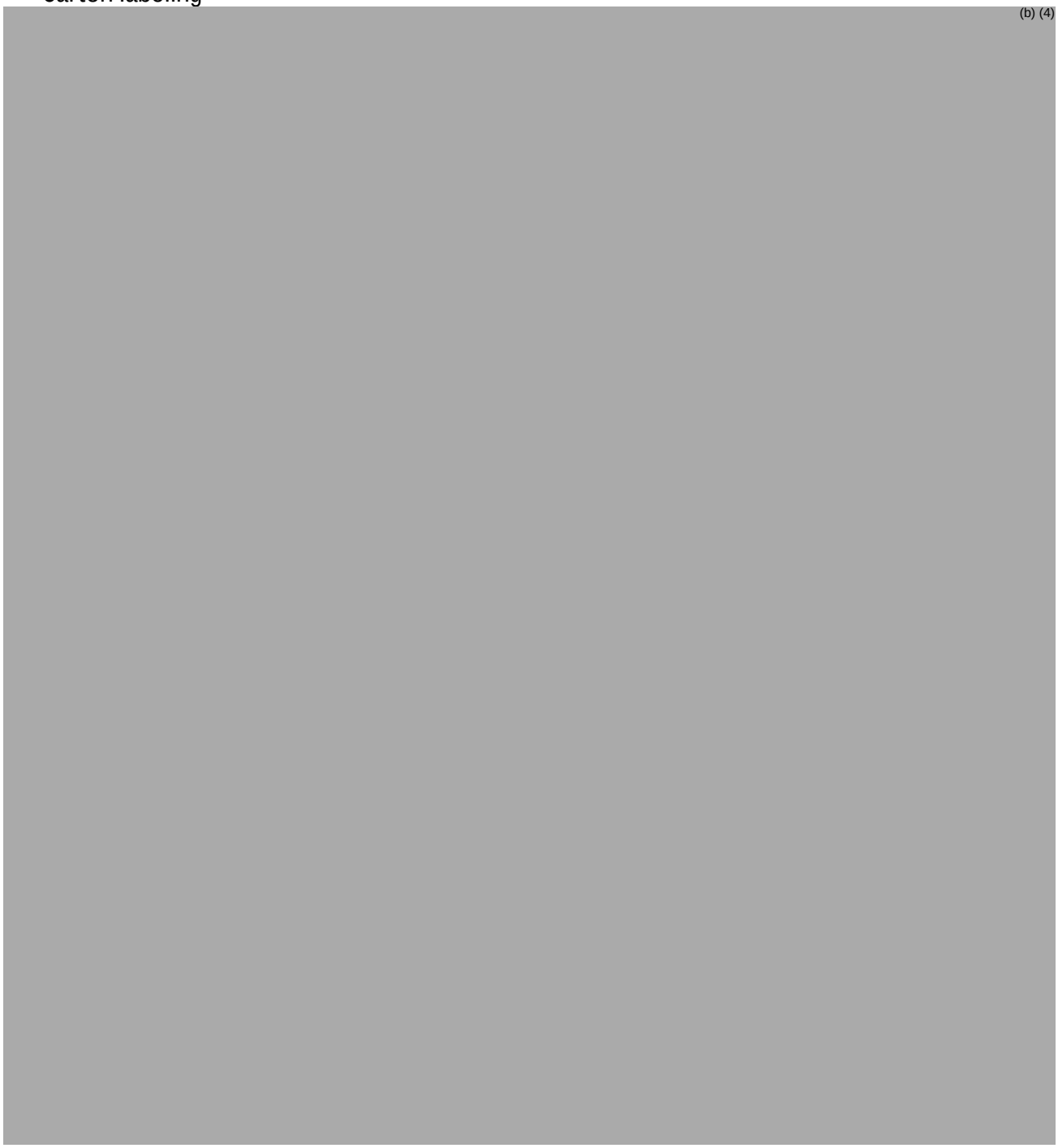
F.2 Label and Labeling Images

Container label (blistercard of 4 tablets)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton labeling

(b) (4)



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEBORAH E MYERS
01/27/2021 01:39:18 PM

IRENE Z CHAN
01/27/2021 06:42:57 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214900
Submission Number	001
Submission Date	10/1/2020
Date Consult Received	10/16/2020
Drug Name	Ibrexafungerp (SCY-078)
Indication	Treatment of vulvovaginal candidiasis
Therapeutic dose	300 mg twice a day for one day, for a total treatment dosage of 600 mg; with or without food.
Clinical Division	DAI

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 10/16/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 107521 dated 09/12/2018 in DARRTS;
- Proposed label (Submission 0001);
- QT evaluation report checklist (Submission 0004);
- Summary of clinical pharmacology studies (Submission 0001);
- SCY-078-106 clinical study report and cardiac safety report (IND 120869, Submission 0040);
- Investigator's brochure (IND 107521, Submission 0176); and
- Highlights of clinical pharmacology and cardiac safety (Submission 0003).

1 SUMMARY

No significant QTc prolongation effect of ibrexafungerp was detected in this QT assessment.

The QT effect of ibrexafungerp was evaluated in study SCY-078-106, a double-blind, randomized, placebo-controlled, single-ascending intravenous (IV) dose study in healthy volunteers. The study covers more than 5-times the therapeutic exposure and two-times the worst-case exposure scenario (CYP3A inhibition, section 3.1) known at this stage, and therefore supports waiving the requirement for inclusion of a separate positive control.

The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that ibrexafungerp is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (sections 3.1.2), by-time analysis (section 4.3), and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF	90% CI
QTc	Ibrexafungerp 125 mg, 1-hr IV	1,548	-2.3	(-4.1 to -0.4)
QTc	Ibrexafungerp 375 mg, 2-hr IV	2,128	-2.8	(-5.0 to -0.7)
QTc	Ibrexafungerp 375 mg, 1-hr IV	3,236	-3.9	(-6.9 to -1.0)
QTc	Ibrexafungerp 250 mg, 1-hr IV	3,489	-4.2	(-7.4 to -1.0)

For further details on the FDA analysis, please see section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~) as a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At a concentration of 5 times ~~or greater than~~ the concentration ~~that~~ achieved after a single day 300 mg BID dose, ibrexafungerp does not prolong the QTc interval to any clinically relevant extent.
Reviewer's comment: *We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The IRT reviewed the QT assessment proposal based on study SCY-078-106 (under IND (b) (4) DARRTS 09/12/2018) and concluded that the study could serve as an alternative to the TQT study. The adequacy of dose/exposure is a review issue.

Part 1 of study SCY-078-106 was a double-blind, randomized, placebo-controlled, alternating-panel, single-ascending-IV dose study in 16 healthy subjects (8 subjects in

each of the two panels). Periods / doses in Panel A was 30 mg, 125 mg, and 375 mg or matching placebo, and in Panel B was 60 mg, 250 mg, and 500 mg (revised to 375 mg) or matching placebo. There was a 7-day washout period between doses for any given subject. Only data from period 2 and 3 were used in the concentration-QTc analysis. 5 subjects provided QT/QTc data at the 125 mg or 250 mg dose level (1-hr infusion), 8 subjects provided data at the 375 mg dose level (6 with 1-hr infusion and 2 with 2-hr infusion), and 6 subjects provided placebo data.

Table 5: Sample Randomization Schedule for Part 1 (SCY-078-106)

Part	Panel	Number of Subjects	Period 1	Period 2	Period 3
I	A[a, b, c]	2	Placebo	125 mg	375 mg
		2	30 mg	Placebo	375 mg
		2	30 mg	125 mg	Placebo
		2	30 mg	125 mg	375 mg
	B[a, b, c, d]	2	Placebo	250 mg	375 mg
		2	60 mg	Placebo	375 mg
		2	60 mg	250 mg	Placebo
		2	60 mg	250 mg	375 mg

Source: SCY-078-106 clinical study report

The primary analysis, primary endpoint, and therapeutic dose have not changed. The estimated therapeutic Cmax is approximately 50% higher, however, the study still provides >5-fold coverage for the therapeutic Cmax (629 ng/mL) and >2-fold coverage for the high clinical exposure scenario (i.e., geometric mean ratio=2.52 in the presence of strong CYP3A4 inhibitor). The hepatic impairment study has been initiated. At the time of this review, no relevant metabolite are identified.

3.1.2 Nonclinical Safety Pharmacology Assessments

Although ibrexafungerp inhibited IKr (hERG current) with an IC50 value of 0.88 µg/mL, there was no QT/QTc interval prolongation in dogs at doses up to 45 mg/kg with plasma concentrations up to ≈22 µg/mL after IV administration (TT094710 and TT085246).

Reviewer's comment: *The estimated Cmax after 2 doses of 300 mg BID in the fed state is 629 ng/mL. Protein binding is reported to be >99%. The ratio between hERG IC50 and free Cmax is >140-fold.*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for ibrexafungerp was based on exposure-response analysis. Please see section 3.2.3 for additional details.

Sponsor's by-time analysis plan is described below:

For each timepoint, an analysis of covariance (ANCOVA) model was fitted for QTcF with the change-from-baseline QTcF (ΔQTcF) as dependent variable, treatment (each dose of SCY- 078 or placebo) as factor, and baseline QTcF as a covariate. Subjects dosed

with placebo were analyzed as a pooled group. From this analysis, the least-squares (LS) mean, and 2-sided 90% CI were calculated for the contrasts "SCY-078 - placebo" for each treatment and timepoint, separately. For HR, PR, QRS, RR, and QT interval, the analysis was based on the change-from-baseline post-dosing (ΔHR, ΔPR, ΔQRS, ΔRR, and ΔQT). The same model was used as described for QTcF.

Reviewer's comment: *By-time analysis results are not interpretable due to small sample size. The reviewer provided non-parametric descriptive statistics to show the by-time trend. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *No outliers were observed in FDA reviewer's analysis.*

3.2.3 Exposure-Response Analysis

The relationship between ΔQTcF and SCY-078 plasma concentrations from doses 120 mg, 250 mg and 375 mg was investigated by a linear mixed-effects modeling approach, that is, ΔQTcF ~ Conc + Treat + Time, and a random intercept per subject. The slope of the relationship between SCY-078 and ΔQTcF was not statistically significant and the predicted ΔΔQTcF effect was -3.67 msec (90% CI: -6.35 to -0.99) or -4.25 msec (90% CI: -7.41 to -1.09) at the observed geometric mean peak plasma concentrations after the 375 mg and 250 mg doses, respectively.

Reviewer's comment: *Results from the reviewer's analysis are similar to the sponsor's.*

3.2.4 Cardiac Safety Analysis

No cardiac-related TEAEs were reported.

There were no deaths or serious adverse events reported during this study. One significant adverse event of severe hypersensitivity occurred during the Period 2 125 mg IV dose in Subject No. (b) (6) This subject completed Panel A- Period 1 (30 mg SCY-078) and Period 2 (125 mg SCY-078) and was discontinued due to severe/related hypersensitivity.

There were no clinically significant changes in vital signs or ECG parameters.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

QT bias assessment was conducted by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (active/placebo/overall) is presented for QTcF (Table 2). This analysis does not suggest the presence of significant negative treatment bias.

Table 2: QTcF bias assessment by treatment

Treatment	# of ECGs	mean (sd), msec	Slope [95% CI], msec per 100 msec
All	2912	-3.58 (6.89)	-1.83 [-3.08 to -0.57]
Ibrexafungerp	2207	-2.82 (6.95)	-2.65 [-4.17 to -1.12]
Placebo	705	-5.96 (6.12)	-8.29 [-9.99 to -6.58]

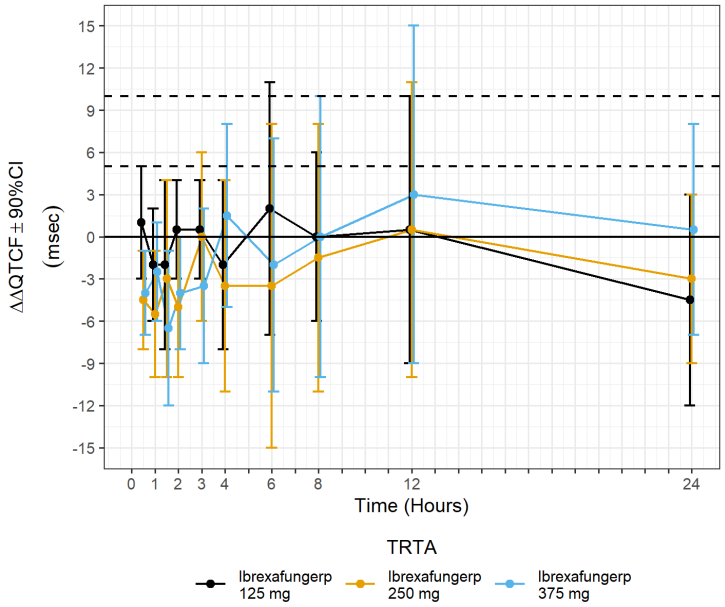
4.3 BY TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. Hour 2.5 data was excluded from the by-time analysis because there were only three subjects at that time point in one period and no subject in another period. The statistical reviewer evaluated the ΔQTcF, ΔHR, ΔPR and ΔQRS effect using nonparametric descriptive statistics. By-time analysis results are not interpretable due to small sample size.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTc for different treatment groups.

Figure 1: Median and 90% CI of ΔΔQTcF Time Course (unadjusted CIs).



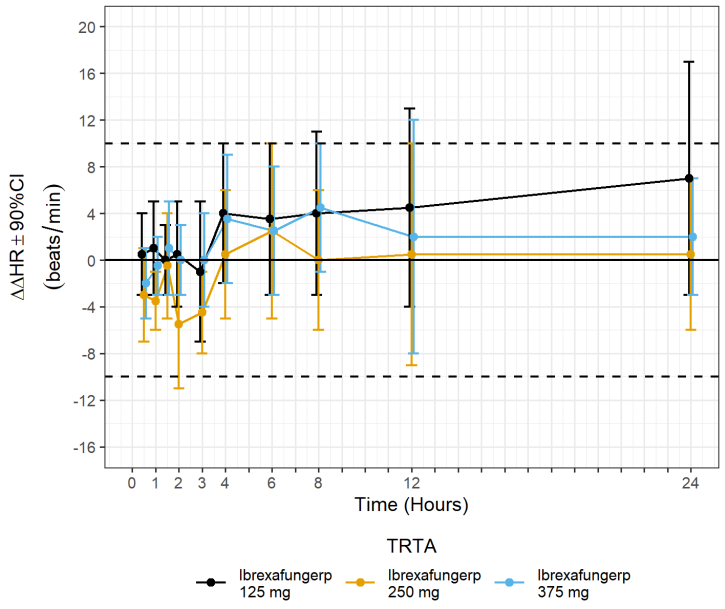
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

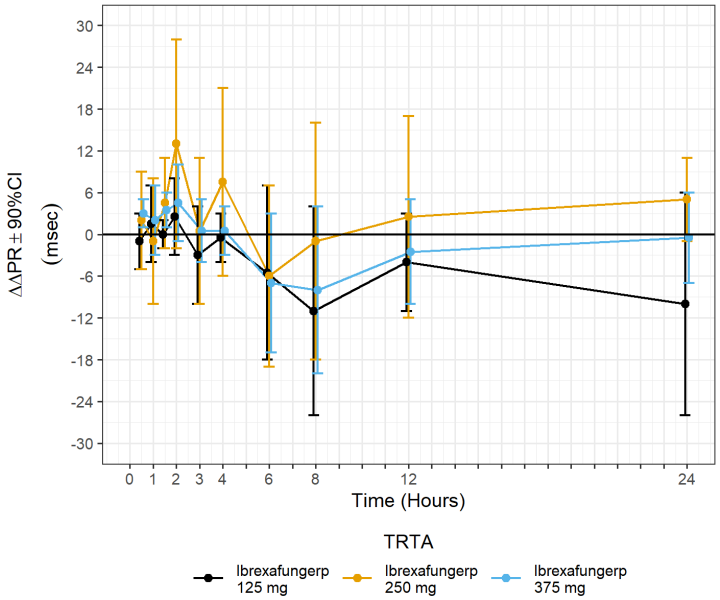
Figure 2: Median and 90% CI of ΔΔHR Time Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

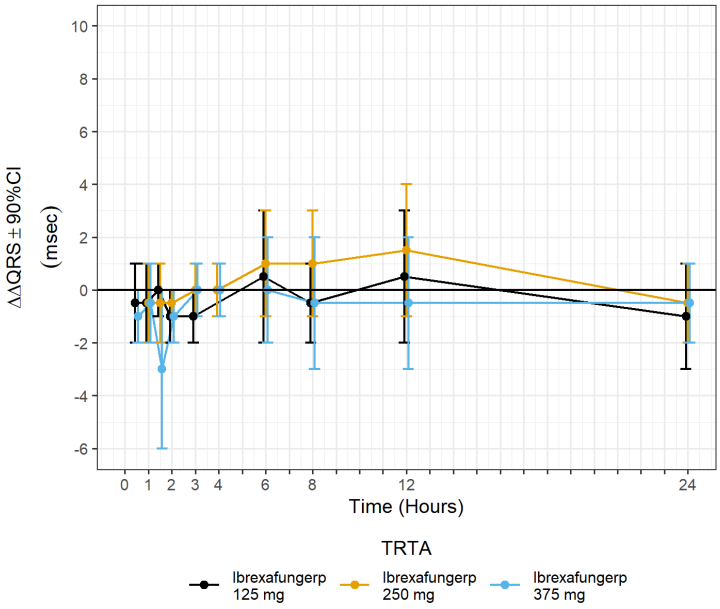
Figure 3: Median and 90% CI of ΔΔPR Time Course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Median and 90% CI of ΔΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF greater than 500 msec or ΔQTcF greater than 60 msec in any dose levels of ibrexafungerp.

4.4.2 HR

None of the subjects experienced HR greater than 100 beats/min in any dose levels of ibrexafungerp.

4.4.3 PR

None of the subjects experienced PR greater than 220 msec in any dose levels of ibrexafungerp.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec in any dose levels of ibrexafungerp.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK. In sensitivity analyses, data from the 2-hr infusion treatment (2 subject at 375 mg dose level and 1 subject on placebo) were excluded.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and ΔΔQTc and 3) presence of non-linear relationship.

Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes. Figure 5 evaluates the time-course of drug-concentration and ΔΔQTc and do not appear to show significant hysteresis. Data from 1-hr and 2-hr infusions at 375 mg dose level were pooled in the presentation. Figure 6 shows the relationship between drug concentration and ΔQTc and does not appear to suggest nonlinear relationship.

Figure 5: Time course of drug concentration (top) and QTc (bottom)

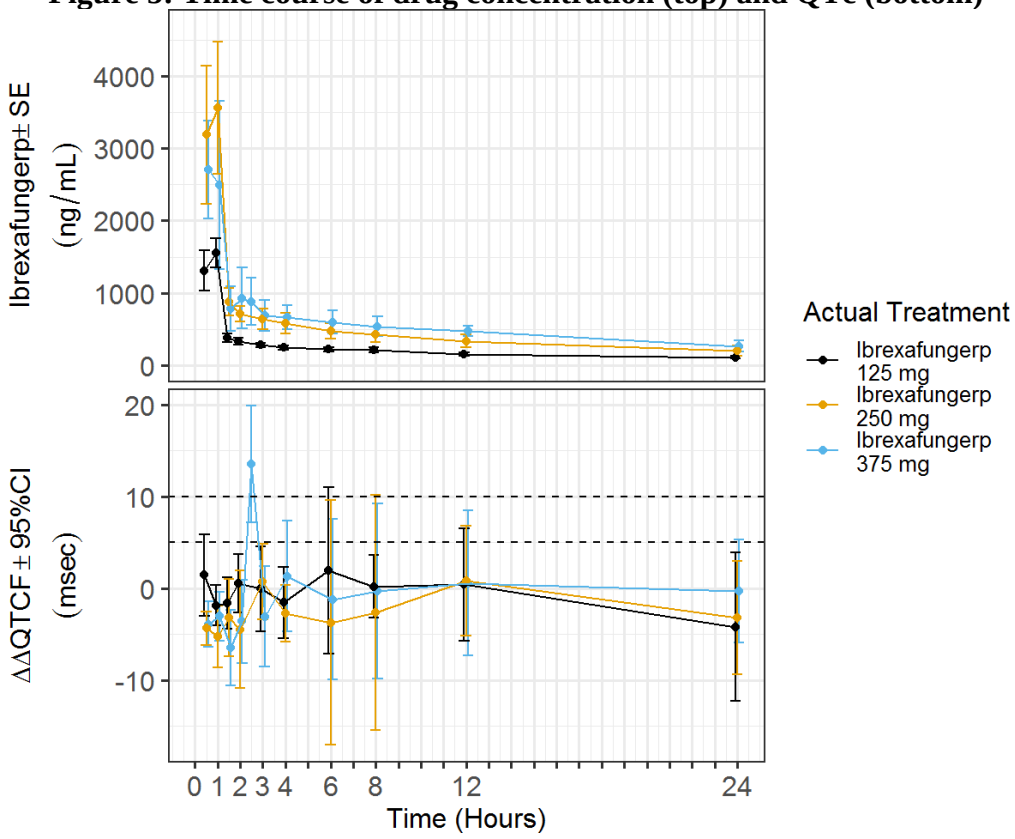
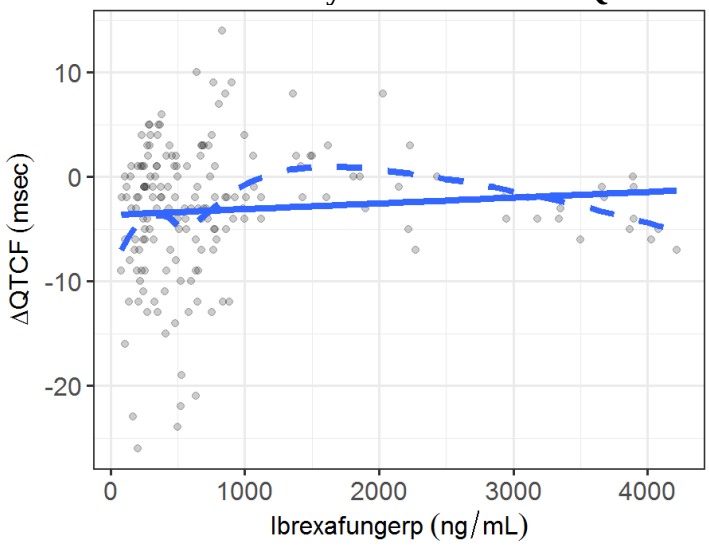
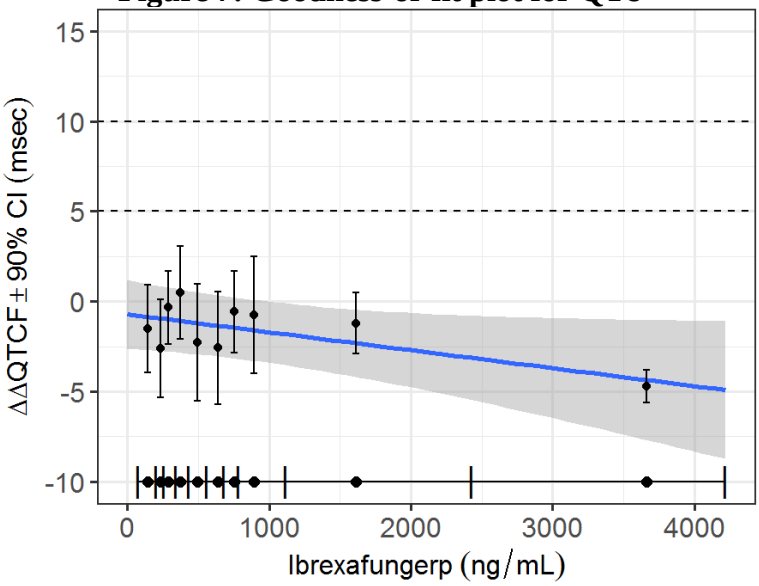


Figure 6: Assessment of linearity of concentration-QTc relationship



The linear model (ΔQTcF ~ 1 + CONC + TIME + treatment + centered baseline, random effect on the intercept) was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 1.

Figure 7: Goodness-of-fit plot for QTc



Additional analysis in which study period was included as a covariate and sensitivity analyses excluding data from 2-hr infusion treatments also suggest a lack of positive exposure-response relationship and the upper bound of 90 CI of predicted QTc change were <10 msec within the studied exposure range.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAN ZHENG
01/11/2021 12:03:56 PM

FERDOUSE BEGUM
01/11/2021 12:57:14 PM

DALONG HUANG
01/11/2021 01:19:09 PM

MICHAEL Y LI
01/11/2021 01:21:50 PM

JOSE VICENTE RUIZ
01/11/2021 01:26:10 PM

CHRISTINE E GARNETT
01/11/2021 01:35:02 PM